Understanding and managing breast milk jaundice

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ABSTRACT

The breastfed infant with prolonged unconjugated hyperbilirubinaemia can present a vexing clinical dilemma. Although it is a frequently observed and usually benign finding, prolonged jaundice in the breastfed newborn requires a thoughtful evaluation that excludes possible pathological aetiologies. While recommendations for the treatment of unconjugated hyperbilirubinaemia in the first 7 days of life are straightforward, the approach to the breastfeeding infant with jaundice that persists beyond the immediate neonatal period is less clearly delineated. A sound understanding of bilirubin physiology and familiarity with current literature must guide the management of the otherwise well breastfeeding infant with prolonged unconjugated hyperbilirubinaemia.

WHAT IS BREAST MILK JAUNDICE?

First described almost 50 years ago, breast milk jaundice, benign unconjugated hyperbilirubinaemia associated with breast feeding, is a common cause of prolonged jaundice in the otherwise healthy breastfed infant born at term.[1–3] Breast milk jaundice presents in the first or second week of life, and can persist for as long as 12 weeks before spontaneous resolution. The incidence of breast milk jaundice in the exclusively breastfed infant during the first 2–3 weeks of life has been reported at 36%.[4] Despite the American Academy of Pediatrics' (AAP) recommendation that exclusive breast feeding continue through the first 6 months of life,[5] breastfeeding interruption is often proposed both as a diagnostic and a therapeutic intervention for breast milk jaundice. Current research, however, does not support the discontinuation of breast feeding in infants with suspected breast milk jaundice. Instead, when indicated, a thoughtful investigation that rules out pathological causes of prolonged unconjugated hyperbilirubinaemia will permit the continuation of uninterrupted breast feeding.

TERMINOLOGY

Several aspects of bilirubin measurement and terminology require explanation. First, a total serum bilirubin of more than 26 µmol/l (1.5 mg/dl) is abnormal, though jaundice in newborn and young infants is not evident on physical examination until levels exceed 86 µmol/l (5 mg/dl).[6] (Please note that conversions between µmol/l and mg/dl have been rounded throughout for simplicity.) In addition, it should be noted that while some laboratories test for serum levels of conjugated and unconjugated bilirubin, other laboratories report direct and indirect bilirubin levels. Direct and indirect serum bilirubin levels are measured via a different method and are close proxies for conjugated bilirubin and unconjugated bilirubin, respectively.[7] Hence, when discussing measured serum bilirubin levels, it is correct to use the terms direct and indirect bilirubin if they are reported in this manner; when discussing bilirubin physiology, only the terms conjugated and unconjugated bilirubin should be used. Finally, threshold levels for testing and treatment in an infant with unconjugated hyperbilirubinaemia always refer to total serum bilirubin (the sum of conjugated plus unconjugated bilirubin, or direct plus indirect bilirubin) rather than unconjugated bilirubin alone.

NEONATAL BILIRUBIN METABOLISM

In the newborn, the majority of unconjugated bilirubin is produced by the breakdown of haemoglobin released from red blood cells and red blood cell precursors. Unconjugated bilirubin is not water soluble and must be conjugated in the liver before excretion in stool. Once bound to albumin in the serum, unconjugated bilirubin can be transported into hepatocytes, where it must be conjugated before it can be excreted into bile. In the hepatocyte, bilirubin undergoes conjugation via the hepatic enzyme UGT 1A1 (uridine diphosphate glucuronosyltransferase 1A1). After excretion from hepatocytes, conjugated bilirubin travels to the small intestine in bile, where intestinal flora convert it to stercobilin for excretion in stool. In the small intestine, however, conjugated bilirubin can be deconjugated by β glucuronidase, an enzyme present in the intestinal brush border. Unconjugated bilirubin is absorbed by the intestinal mucosa and returned to the liver via the portal circulation for reconjugation, a process known as enterohepatic circulation (figure 1).[6]

Physiological jaundice, or jaundice resulting from normal neonatal bilirubin physiology, is commonly encountered in both breastfed and bottle-fed newborns in the first week of life. In the normal newborn, bilirubin synthesis is greatly increased, while hepatic uptake, conjugation and excretion occur less efficiently than in adults. The high blood volume and high haemoglobin concentration of the newborn, combined with a significantly shorter red blood cell lifespan, results in a marked increase in bilirubin production. In addition, neonatal physiology limits bilirubin excretion. The activity of the hepatic enzyme UGT 1A1 is significantly lower in neonates than in adults, resulting in less efficient bilirubin conjugation.[8] Absence of the clostridial gut flora needed for the conversion of bilirubin to stercobilin results in a higher concentration of bilirubin in the intestinal tract. The mucosal enzyme β glucuronidase is more active in the infant small intestine, favouring the process of bilirubin deconjugation. In the setting of the more permeable infant gut wall,

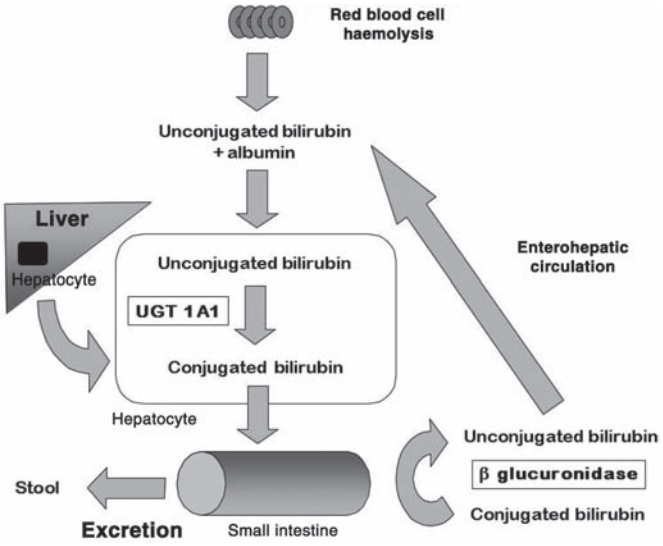

Figure 1 Neonatal bilirubin metabolism.

this high concentration of unconjugated bilirubin results in increased enterohepatic circulation.[6]

The sum effect of these physiological alterations is to produce an elevated unconjugated serum bilirubin concentration, which, in turn, results in visible jaundice in more than half of all normal newborns during the first week of life, regardless of feeding method.[9]

THE PHYSIOLOGY OF BREAST MILK JAUNDICE

Some healthy breast-fed infants will have clinically apparent jaundice that lasts beyond the first week of life or initially presents after the first week of life. Persistent unconjugated hyperbilirubinaemia in otherwise healthy infants may be due to breast milk jaundice, characterised by normal weight gain, normal stool and urine output, an otherwise normal physical examination and no signs or symptoms of underlying pathology. Total serum bilirubin levels in breast milk jaundice alone do not exceed 200 µmol/l (12 mg/dl). When additional contributing factors are present, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency or inherited defects in bilirubin conjugation, levels may be higher and phototherapy may be required.

Breast milk jaundice is a benign condition that resolves without treatment.[10] Clinical experience and quantitative data confirm that when formula is substituted for breast milk, hyperbilirubinaemia rapidly improves.[1–3] Since breastfeeding jaundice was first recognised as a clinical entity, multiple unsuccessful attempts have been made to identify a specific chemical in breast milk that might be responsible for causing breast milk jaundice.[1 2 11–13] Animal models suggest that mature breast milk may increase unconjugated bilirubin levels by enhancing bilirubin uptake in the digestive tract, thus increasing enterohepatic circulation.[4 14] A recent study correlates higher unconjugated bilirubin levels in exclusively breastfed infants with higher levels of epidermal growth factor (EGF) both in the serum of affected infants and in the breast milk of their mothers. Because EGF is thought to enhance absorption in the intestine during the neonatal period, increased levels of EGF may offer a plausible mechanism for increased bilirubin absorption in the gut and resultant unconjugated hyperbilirubinaemia in breast milk jaundice.[15]

PATHOLOGICAL CAUSES OF PROLONGED UNCONJUGATED HYPERBILIRUBINAEMIA

The clinician who suspects breast milk jaundice in an infant with unconjugated hyperbilirubinaemia must first rule out possible underlying pathological causes if (1) jaundice persists past the first week of life or presents after the first week of life and (2) the total serum bilirubin concentration is in excess of 200 µmol/l (12 mg/dl) or is continuing to rise. Diagnosing breast milk jaundice begins with the essential question of whether the infant is breast feeding adequately.

Inadequate breast feeding and neonatal jaundice

In the breastfed neonate, with his baseline physiological limitation in bilirubin metabolism, insufficient breast milk intake can exacerbate jaundice.[7] Inadequate intake of breast milk leads to decreased stool output and increased reabsorption of bilirubin from the gut, resulting in unconjugated hyperbilirubinaemia. Neonates with insufficient breast milk intake may have excessive weight loss or poor weight gain, poor urine and stool output and failure to clear meconium. Elevated levels of bilirubin lead to lethargy and poor feeding, further diminishing the infant's ability to excrete bilirubin in stool. Jaundice in the infant who is breast feeding poorly is a potentially serious condition that requires early identification and treatment to prevent dehydration, malnutrition and dangerously high bilirubin levels, which can result in kernicterus.[6]

Prevention of jaundice due to problems with breast feeding should focus on early support of the mother-infant dyad. Breastfeeding success depends upon breastfeeding initiation in the immediate postpartum period, skin-to-skin contact and rooming-in to prevent separation of mother and baby. Newborns should be put to the breast frequently and should not receive supplemental water or formula. Lactation consultation should be obtained when indicated to optimise latch and milk transfer. Careful monitoring of urine and stool output and daily weight checks provide objective data on whether breast milk intake is sufficient. If there is evidence of insufficient intake, mothers should pump in order to increase breast milk supply, and formula supplementation may be necessary. In the jaundiced infant who is breast feeding poorly, serum bilirubin levels should be followed closely, and phototherapy should be initiated as indicated by AAP guidelines.[7]

Though jaundice that occurs in a breastfed infant as the result of insufficient breast milk intake is commonly referred to as 'breastfeeding jaundice', this term is misleading and should be avoided. We refer to this clinical entity as 'not enough breastfeeding' jaundice because the underlying aetiology is not breast feeding itself but its converse, lack of adequate breast feeding. The nutritional status of the patient, which is poor in not enough breastfeeding jaundice and normal in breast milk jaundice, is the key to distinguishing these two clinically distinct but sometimes coexisting entities. An infant cannot be diagnosed with breast milk jaundice until his nutritional status is normal and breast feeding is well established (table 1).

Prolonged unconjugated hyperbilirubinaemia in the adequately breastfed infant

Before prolonged unconjugated hyperbilirubinaemia in the nutritionally replete breastfeeding infant may be identified as breast milk jaundice, other pathological aetiologies must be ruled out. The presence or absence of haemolysis is an important diagnostic branch point. An infant with evidence of ongoing haemolysis probably has hyperbilirubinaemia as the result

of increased red blood cell breakdown, which releases haemoglobin and results in the increased production of unconjugated bilirubin. Conversely, an infant without evidence of haemolysis may have a defect of bilirubin processing or another underlying condition (table 2). Here it should be noted that a rapidly rising bilirubin (greater than 8.6 µmol/l or 0.5 mg/dl per hour) or jaundice that presents in the first 24 hours of life is not consistent with a diagnosis of breast milk jaundice, and in these cases a pathological aetiology should be pursued.[7]

Unconjugated hyperbilirubinaemia due to haemolysis

As previously noted, newborn infants normally experience increased breakdown of red blood cells and their precursors. In particular, infants with polycythaemia at birth may exhibit exaggerated haemolysis, as may infants with cephalohaematoma or excessive bruising from birth trauma. Additional risk factors for haemolysis in the neonate may include exposure to maternal antigens, as in ABO incompatibility or Rhesus isoimmunisation. While rare, deficiency of one of the many enzymes necessary for glucose metabolism in red blood cells, such as pyruvate kinase, may shorten red blood cell lifespan and increase haemolysis.[16] Finally, red blood cell membrane abnormalities such as hereditary spherocytosis may also predispose infants to increased red blood cell destruction and can present with unconjugated hyperbilirubinaemia in the newborn period.[17] It should be noted that the diagnosis of milder forms of haemolysis in newborns by the traditional methods used in older children and adults is often difficult. Measurement of carbon monoxide production and excretion in breath is a sensitive method for diagnosis of milder forms of haemolysis in newborns, but equipment for the measurement of this low-level increase is, unfortunately, not currently commercially available.

Table 1 "Not enough breastfeeding" jaundice versus breast milk jaundice

	'Not enough breastfeeding' jaundice	Breast milk jaundice
Presentation	First week of life	Late in first to second week of life
Feeding	Feeding poorly	Feeding well
Weight	Excessive weight loss or poor weight gain	Normal weight gain
Urine	Infrequent urine output	Frequent urine output
Stool	Infrequent meconium or transitional stools	Frequent yellow stools
Level of concern	A potentially serious problem	A benign condition
Treatment	Phototherapy if indicated	See algorithm (figure 2)
Resolution	With improved breast milk intake and bilirubin excretion in stools	Spontaneous, within first 12 weeks of life
Breastfeeding management	Provide lactation support Continue breast feeding	Continue breast feeding Trial of breastfeeding interruption not recommended for diagnosis

Table 2 Causes of prolonged unconjugated hyperbilirubinaemia

Evidence of haemolysis	No evidence of haemolysis
Neonatal conditions	**Neonatal conditions**
Bruising	Not enough breast feeding
Cephalohaematoma	Breast milk
Polycythaemia	G6PD deficiency causing jaundice
ABO incompatibility	**Conjugation defects**
Rh incompatibility	UGT 1A1 promoter defects
Red blood cell enzyme abnormality	Crigler-Najjar syndrome types I and II
G6PD deficiency causing haemolytic crisis	**Other**
Pyruvate kinase deficiency	Galactosaemia
Other enzyme deficiencies	Hypothyroidism
Red blood cell membrane defect	Intestinal obstruction
Hereditary spherocytosis	Pyloric stenosis
Other membrane defects	Medications

G6PD, glucose-6-phosphate dehydrogenase; Rh, rhesus; UGT 1A1, uridine diphosphate glucuronosyltransferase.

Unconjugated hyperbilirubinaemia due to G6PD deficiency

Deficiency of another red blood cell enzyme, G6PD, is an important consideration in infants presenting with prolonged unconjugated hyperbilirubinaemia. G6PD deficiency is a common condition that affects an estimated 4.9% of the world's population, from Africa to Asia and the Mediterranean to South America.[18] In a recent study conducted in the USA, 12.2% of African American men and 4.3% of Asian American men were G6PD deficient.[19] Although it is an X-linked trait, G6PD deficiency affects female as well as male carriers, owing to the variable inactivation of X chromosomes and also to the rare existence of the defect on both X chromosomes. More than 140 different mutations have been identified as causing G6PD deficiency. As a result, the clinical presentation of G6PD deficiency can vary from chronic haemolytic anaemia to normal enzyme activity. Illness, stress, certain medications (notably sulphonamides) and other substances (fava beans, mothballs and henna) can precipitate a haemolytic crisis in those with G6PD deficiency; hence early diagnosis of this condition can be of great benefit to patients.[20 21]

Recently published data from the US Kernicterus Registry demonstrates that 20% of the 125 infants included in the registry had diagnosed G6PD deficiency.[22] Therefore, understanding the role of G6PD deficiency in hyperbilirubinaemia and testing when appropriate is an essential component in the investigation of the infant with prolonged unconjugated hyperbilirubinaemia. Clinicians should be aware that the presentation of hyperbilirubinaemia in the G6PD-deficient infant is heterogeneous. Patients in whom a haemolytic crisis has been triggered by an exposure may have rapid onset of profound jaundice and evidence of haemolysis. Alternatively, G6PD-deficient infants may have prolonged unconjugated hyperbilirubinaemia with a more insidious onset. These infants may lack evidence of frank haemolysis, even in the setting of dangerously high bilirubin levels. In these cases, hyperbilirubinaemia may be due to a synergistic combination of impaired bilirubin conjugation and low-level haemolysis due to G6PD deficiency.[23–25]

Unconjugated hyperbilirubinaemia in the absence of haemolysis

Defects in hepatic bilirubin conjugation may cause prolonged unconjugated hyperbilirubinaemia without evidence of haemolysis. In addition, a handful of other conditions may underlie the presentation of prolonged unconjugated hyperbilirubinaemia in the infant with neither conjugation defects nor haemolysis.

UGT 1A1 mutations

Mutations in the gene coding for UGT 1A1, the enzyme responsible for bilirubin conjugation, can reduce its activity

and impair conjugation in both breastfed and formula-fed infants, as well as in older children and adults. Multiple UGT 1A1 mutations have been identified, and now are known to cause a spectrum of disorders. In the most severe of these, Crigler-Najjar syndrome, mutations in the UGT 1A1 gene result in inability to synthesise this enzyme adequately. Crigler-Najjar syndrome is inherited in an autosomal recessive pattern and is an uncommon disorder, occurring in one in one million infants. In Crigler-Najjar type I, infants cannot produce UGT 1A1 and present in the neonatal period with critically high serum levels of unconjugated bilirubin, which can lead to kernicterus and death. Because some UGT 1A1 activity is preserved in Crigler-Najjar type II, this disease can have a more indolent course, with serum bilirubin levels that are elevated but rarely reach the threshold for phototherapy. In addition, patients with Crigler-Najjar type II usually respond to treatment with phenobarbital, which induces UGT 1A1.[26]

Gilbert's syndrome represents the least severe of the continuum of disorders caused by UGT 1A1 mutations. In Gilbert's, functional UGT 1A1 is produced, but at levels one-third to one-tenth of normal. As a result, adolescents and adults with Gilbert's exhibit self-resolving symptoms of mild jaundice that appear when patients are hungry, tired or ill. In adults, bilirubin levels vary, but rarely exceed 50 µmol/l (3 mg/dl). Mutations in the UGT 1A1 gene causing Gilbert's syndrome are common, resulting in an estimated overall prevalence of ≥8% of Gilbert's in populations studied.[27]

Infants who carry one of the UGT 1A1 mutations responsible for Gilbert's may also exhibit abnormalities in bilirubin metabolism. Regardless of feeding method, infants who are homozygous for an UGT 1A1 mutation have been found to have subtle elevations in bilirubin levels in the first week of life.[28 29] In addition, the presence of an UGT 1A1 mutation may exacerbate neonatal hyperbilirubinaemia in infants with G6PD deficiency, ABO incompatibility or hereditary spherocytosis.[30–32]

Although prolonged unconjugated hyperbilirubinaemia has been reported in formula-fed infants carrying UGT 1A1 mutations, exclusively breastfed infants are far more likely to present with this clinical picture.[33 34] Nevertheless, not all breastfed infants carrying UGT 1A1 mutations exhibit breast milk jaundice, and breast milk jaundice can occur in infants with normal UGT 1A1. It is likely that in some breastfed infants, the combined effect of an UGT 1A1 mutation together with the presence of breast milk may lead to jaundice that is more clinically apparent and slower to resolve.

Other non-haemolytic aetiologies

Note should be made of several other conditions that can cause prolonged unconjugated hyperbilirubinaemia in the infant with normal bilirubin metabolism and no evidence of haemolysis. Galactosaemia, the deficiency of galactose-1-phosphate uridyltransferase that results in an inability to metabolise the galactose found in both breast milk and cow's milk, can present with prolonged unconjugated hyperbilirubinaemia, although conjugated hyperbilirubinaemia is more common.[35 36] Hypothyroidism has been described in association with prolonged unconjugated hyperbilirubinaemia, although the mechanism for this is not known.[37]

Pyloric stenosis can sometimes present with unconjugated hyperbilirubinaemia, and infants with pyloric stenosis and mutations of UGT 1A1 have been shown to be more likely to present with jaundice.[38] Prolonged hyperbilirubinaemia in patients with annular pancreas or duodenal or jejunal atresia has also been described.[39] In addition, unconjugated hyperbilirubinaemia is sometimes clinically evident in infants with sepsis or urinary tract infection, though jaundice is neither a sensitive nor a specific sign for these conditions. Finally, some medications, notably ceftriaxone, dicloxicillin and the sulphonamides, have been implicated in displacing bilirubin from albumin and thus impairing bilirubin conjugation, although this is an area of controversy.[40 41]

INVESTIGATION OF PROLONGED UNCONJUGATED HYPERBILIRUBINAEMIA IN THE BREASTFED INFANT

Determination of unconjugated (indirect) and conjugated (direct) serum bilirubin levels is an essential first step in the investigation of the breastfed infant with prolonged jaundice (figure 2). Conjugated hyperbilirubinaemia is never normal, and is indicative of other possible serious aetiologies such as biliary atresia, neonatal hepatitis and other disorders of bilirubin excretion. If conjugated bilirubin is less than 17 µmol/l (1 mg/dl) or less than 20% of the total bilirubin, it is considered normal. In the presence of a normal conjugated bilirubin, a total serum bilirubin of 200 µmol/l (12 mg/dl) is the level at which further evaluation should be initiated, as hyperbilirubinaemia caused by breast milk alone should not exceed this level. In the case of an infant with prolonged unconjugated hyperbilirubinaemia whose total bilirubin exceeds 200 µmol/l (12 mg/dl), additional testing should first focus on ruling out haemolysis via haematocrit or haemoglobin, reticulocyte count, direct Coombs' testing and peripheral blood smear.

Clinicians should maintain a low threshold to test for G6PD deficiency. Patients of African, Asian, Latino, Mediterranean and Middle Eastern descent are at risk for G6PD deficiency, but patients of any ethnicity should be tested if there is evidence of haemolysis or if indirect serum bilirubin exceeds 200 µmol/l (12 mg/dl) (table 3).

It should be noted that the presence of a high percentage of young red blood cells, which contain more G6PD than older cells, may mask a deficiency, as can the release of G6PD from lysed red blood cells.[20 23] If clinical suspicion remains high, retesting for G6PD deficiency once jaundice has resolved may be indicated.[7]

In addition to evaluating for haemolysis, other non-haemolytic causes of prolonged unconjugated hyperbilirubinaemia should be considered. The newborn screen should be carefully reviewed to rule out hypothyroidism and galactosaemia. Owing to the small possibility of a false-negative newborn screen, thyroid function testing should be repeated if clinical concern exists for hypothyroidism.[42]

Screening for urinary tract infection in the asymptomatic infant with prolonged jaundice is another area of controversy. While elevated rates of urinary tract infection have been found in otherwise asymptomatic infants presenting with prolonged unconjugated hyperbilirubinaemia, the significance of these results has been disputed.[43–45] In afebrile infants with prolonged unconjugated hyperbilirubinaemia and no signs or symptoms of urinary tract infection, further testing is not indicated.

Testing for the many known mutations of UGT 1A1 is not readily available, but the diagnosis of Gilbert's may be confirmed by obtaining serum bilirubin levels from the infant's parents. Elevated indirect bilirubin in either parent supports the diagnosis of an UGT 1A1 mutation as the cause of prolonged unconjugated hyperbilirubinaemia in the breastfed infant.

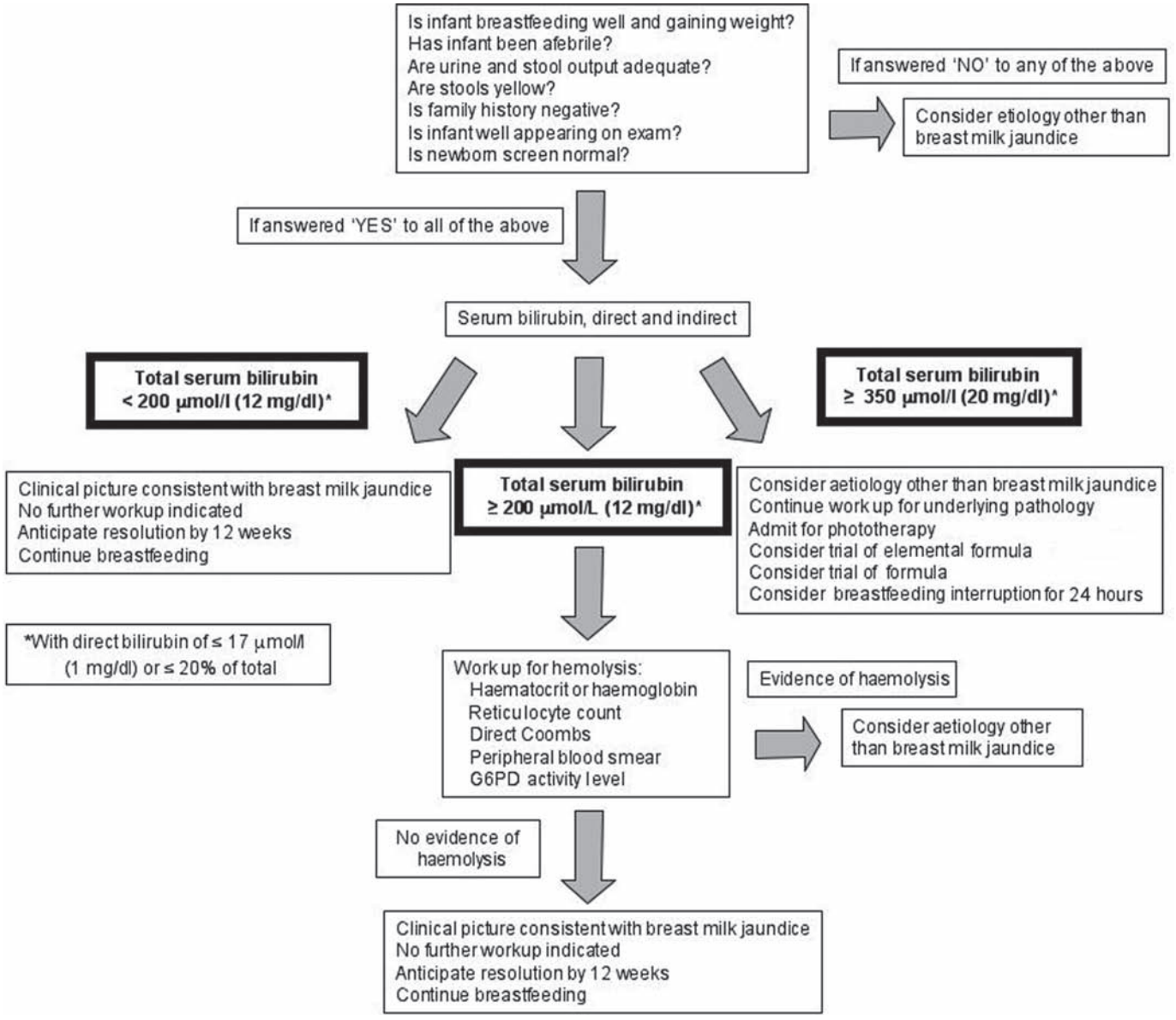

Figure 2 Investigation of the infant with suspected breast milk jaundice.

Table 3 Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency in breastfed infants with prolonged unconjugated hyperbilirubinaemia

Any infant of the following ethnic descent:
African
Asian
Latino
Mediterranean
Middle Eastern
Any infant with family history of G6PD deficiency
Any infant with evidence of haemolysis
Any infant with prolonged indirect hyperbilirubinaemia and total serum bilirubin ≥200 µmol/l (12 mg/dl)

MANAGEMENT OF BREAST MILK JAUNDICE

The interruption of breast feeding to diagnose breast milk jaundice is not advised. A cessation of breast feeding, however brief, may jeopardise an infant's ability to return to exclusive breast feeding, which is unnecessarily harmful to the infant and traumatic for parents. Even beyond the risks to continued successful breast feeding, however, a trial of breastfeeding cessation may be falsely reassuring and may obscure a potentially serious underlying aetiology for prolonged hyperbilirubinaemia. For example, a breastfed infant in whom breast milk jaundice occurs concomitantly with G6PD deficiency may exhibit clinical improvement in jaundice when breast feeding is discontinued, and a potentially significant underlying condition may go undiagnosed.

Infants with breast milk jaundice require no treatment if clinically well and if the total serum bilirubin concentration remains below that recommended for phototherapy. If total bilirubin exceeds 200 µmol/l (12 mg/dl), further investigation is required as described above, and the diagnosis of breast milk jaundice alone cannot be made. In the event of a negative investigation and persistent hyperbilirubinaemia above 200 µmol/l (12 mg/dl), the possibility of the additional presence of an UGT 1A1 mutation or G6PD deficiency should be strongly considered. For total serum bilirubin over 350 µmol/l (20 mg/dl), treatment with phototherapy is recommended. In well-appearing breastfed infants whose total serum bilirubin

concentrations are approaching this level, a trial of supplementation with formula or a 24-hour interruption of breast feeding should be considered, and an alternative or additional aetiology for the infant's condition should be aggressively pursued.[46]

CONCLUSION

In an infant who is otherwise well, breast milk jaundice is a benign and self-limited condition. The diagnosis of breast milk jaundice can be made based on clinical appearance, time course, bilirubin levels and further testing as indicated. Interruption of breast feeding is not recommended as a diagnostic or a therapeutic intervention. Once pathological aetiologies are ruled out, further evaluation is unnecessary.

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